

Exhibit C



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INTERIM UPDATE

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INTERIM UPDATE: This Practice Bulletin is updated as highlighted to clarify the guidance on the assessment of hCG levels after uterine aspiration in women with a pregnancy of unknown location.

Tubal Ectopic Pregnancy

Ectopic pregnancy is defined as a pregnancy that occurs outside of the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube. Most cases of tubal ectopic pregnancy that are detected early can be treated successfully either with minimally invasive surgery or with medical management using methotrexate. However, tubal ectopic pregnancy in an unstable patient is a medical emergency that requires prompt surgical intervention. The purpose of this document is to review information on the current understanding of tubal ectopic pregnancy and to provide guidelines for timely diagnosis and management that are consistent with the best available scientific evidence.

Background

Epidemiology

According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies (1). However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992 (1). Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality (2). The prevalence of ectopic pregnancy among women presenting to an emergency department with first-trimester vaginal bleeding, or abdominal pain, or both, has been reported to be as high as 18% (3).

Etiology

The fallopian tube is the most common location of ectopic implantation, accounting for more than 90% of cases (4). However, implantation in the abdomen (1%), cervix (1%), ovary (1–3%), and cesarean scar (1–3%)

can occur and often results in greater morbidity because of delayed diagnosis and treatment (4). An ectopic pregnancy also can co-occur with an intrauterine pregnancy, a condition known as heterotopic pregnancy. The risk of heterotopic pregnancy among women with a naturally achieved pregnancy is estimated to range from 1 in 4,000 to 1 in 30,000, whereas the risk among women who have undergone in vitro fertilization is estimated to be as high as 1 in 100 (5, 6).

Risk Factors

One half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors (3). Women with a history of ectopic pregnancy are at increased risk of recurrence. The chance of a repeat ectopic pregnancy in a woman with a history of one ectopic pregnancy is approximately 10% (odds ratio [OR] 3.0; 95% CI, 2.1–4.4). In a woman with two or more prior ectopic pregnancies, the risk of recurrence increases to more than 25% (OR, 11.17; 95% CI, 4.0–29.5) (3). Other important risk factors for ectopic pregnancy include previous damage to the fallopian tubes, factors secondary to ascending pelvic infection, and prior pelvic or fallopian tube surgery (3, 7). Among women who become pregnant through the use of assisted reproductive technology, certain factors such as tubal factor infertility and multiple

embryo transfer are associated with an increased risk of ectopic pregnancy (8, 9). Women with a history of infertility also are at increased risk of ectopic pregnancy independent of how they become pregnant (7). Other less significant risk factors include a history of cigarette smoking and age older than 35 years (7).

Women who use an intrauterine device (IUD) have a lower risk of ectopic pregnancy than women who are not using any form of contraception because IUDs are highly effective at preventing pregnancy. However, up to 53% of pregnancies that occur with an IUD in place are ectopic (10). Factors such as oral contraceptive use, emergency contraception failure, previous elective pregnancy termination, pregnancy loss, and cesarean delivery have not been associated with an increased risk of ectopic pregnancy (3, 7, 11, 12).

Clinical Considerations and Recommendations

► *How is an ectopic pregnancy diagnosed?*

The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.

Women with clinical signs and physical symptoms of a ruptured ectopic pregnancy, such as hemodynamic instability or an acute abdomen, should be evaluated and treated urgently. Early diagnosis is aided by a high index of suspicion. Every sexually active, reproductive-aged woman who presents with abdominal pain or vaginal bleeding should be screened for pregnancy, regardless of whether she is currently using contraception (13, 14). Women who become pregnant and have known significant risk factors should be evaluated for possible ectopic pregnancy even in the absence of symptoms.

Transvaginal Ultrasonography

Ultrasonography can definitively diagnose an ectopic pregnancy when a gestational sac with a yolk sac, or embryo, or both, is noted in the adnexa (15, 16); however, most ectopic pregnancies do not progress to this stage (15). The ultrasound findings of a mass or a mass with a hypoechoic area that is separate from the ovary should raise suspicion for the presence of an ectopic pregnancy; however, its positive predictive value is only 80% (15) because these findings can be confused with pelvic structures, such as a paratubal cyst, corpus luteum, hydrosalpinx, endometrioma, or bowel. Although an early intrauterine gestational sac may be visualized as early as 5 weeks of gestation (17), definitive ultrasound evidence of an intrauterine pregnancy includes visual-

ization of a gestational sac with a yolk sac or embryo (16). Visualization of a definitive intrauterine pregnancy eliminates ectopic pregnancy except in the rare case of a heterotopic pregnancy. Although a hypoechoic “sac-like” structure (including a “double sac sign”) (18) in the uterus likely represents an intrauterine gestation, it also may represent a pseudogestational sac, which is a collection of fluid or blood in the uterine cavity that is sometimes visualized with ultrasonography in women with an ectopic pregnancy (19, 20).

Serum Human Chorionic Gonadotropin Measurement

Measurement of the serum hCG level aids in the diagnosis of women at risk of ectopic pregnancy. However, serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient’s history, symptoms, and ultrasound findings (21, 22). Accurate gestational age calculation, rather than an absolute hCG level, is the best determinant of when a normal pregnancy should be seen within the uterus with transvaginal ultrasonography (23, 24). An intrauterine gestational sac with a yolk sac should be visible between 5 weeks and 6 weeks of gestation regardless of whether there are one or multiple gestations (25, 26). In the absence of such definitive information, the serum hCG level can be used as a surrogate for gestational age to help interpret a nondiagnostic ultrasonogram.

The “discriminatory level” is the concept that there is a hCG value above which the landmarks of a normal intrauterine gestation should be visible on ultrasonography. The absence of a possible gestational sac on ultrasound examination in the presence of a hCG measurement above the discriminatory level strongly suggests a nonviable gestation (an early pregnancy loss or an ectopic pregnancy). In 50–70% of cases, these findings are consistent with an ectopic pregnancy (27–29). However, the utility of the hCG discriminatory level has been challenged (24) in light of a case series that noted ultrasonography confirmation of an intrauterine gestational sac on follow-up when no sac was noted on initial scan and the serum hCG level was above the discriminatory level (30–32). If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue (24, 32). Women with a multiple gestation have higher hCG levels than those with a single gestation at any given gestational age and may have hCG levels above traditional discriminatory hCG levels before ultrasonography recognition (24).

Trends of Serial Serum Human Chorionic Gonadotropin

A single hCG concentration measurement cannot diagnose viability or location of a gestation. Serial hCG concentration measurements are used to differentiate normal from abnormal pregnancies (21, 22, 33, 34). When clinical findings suggest an abnormal gestation, a second hCG value measurement is recommended 2 days after the initial measurement to assess for an increase or decrease. Subsequent assessments of hCG concentration should be obtained 2–7 days apart, depending on the pattern and the level of change.

In early pregnancy, serum hCG levels increase in a curvilinear fashion until a plateau at 100,000 mIU/mL by 10 weeks of gestation. Guidelines regarding the minimal increase in hCG for a potentially viable intrauterine pregnancy have become more conservative (ie, slower increase) (21, 22) and have been demonstrated to be dependent on the initial value (35). There is a slower than expected increase in serum hCG levels for a normal gestation when initial values are high. For example, the expected rate of increase is 49% for an initial hCG level of less than 1,500 mIU/mL, 40% for an initial hCG level of 1,500–3,000 mIU/mL, and 33% for an initial hCG level greater than 3,000 mIU/mL (35). In early pregnancy, an increase in serum hCG of less than a minimal threshold in 48 hours is suspicious of an abnormal pregnancy (ectopic or early pregnancy loss) because 99% of normal intrauterine pregnancies will have a rate of increase faster than this minimum. However, even hCG patterns consistent with a growing or resolving gestation do not eliminate the possibility of an ectopic pregnancy (36).

Decreasing hCG values suggest a failing pregnancy and may be used to monitor spontaneous resolution, but this decrease should not be considered diagnostic. Approximately 95% of women with a spontaneous early pregnancy loss will have a decrease in hCG concentration of 21–35% in 2 days depending on initial hCG levels (34). A woman with decreasing hCG values and a possible ectopic pregnancy should be monitored until nonpregnant levels are reached because rupture of an ectopic pregnancy can occur while levels are decreasing or are very low.

Pregnancy of Unknown Location

A pregnant woman without a definitive finding of an intrauterine or ectopic pregnancy on ultrasound examination has a “pregnancy of unknown location” (37). A pregnancy of unknown location should not be considered a diagnosis, rather it should be treated as a transient state and efforts should be made to establish a definitive diag-

nosis when possible (16). A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management (22, 37). Follow-up to confirm a diagnosis of ectopic pregnancy in a stable patient, especially at first clinical encounter, is recommended to eliminate misdiagnosis and to avoid unnecessary exposure to methotrexate, which can lead to interruption or teratogenicity of an ongoing intrauterine pregnancy (16, 38, 39). The first step is to assess for the possibility that the gestation is advancing.

When the possibility of a progressing intrauterine gestation has been reasonably excluded, uterine aspiration can help to distinguish early intrauterine pregnancy loss from ectopic pregnancy by identifying the presence or absence of intrauterine chorionic villi. Choosing the appropriate time and intervention should be done through shared decision making, incorporating the patient’s values and preferences regarding maternal risk and the possibility of interrupting a progressing pregnancy. If chorionic villi are found, then failed intrauterine pregnancy is confirmed and no further evaluation is necessary. If chorionic villi are not confirmed, hCG levels should be monitored, with the first measurement taken 12–24 hours after aspiration. A plateau or increase in hCG postprocedure suggests that evacuation was incomplete or there is a nonvisualized ectopic pregnancy, and further treatment is warranted. Although the change at which hCG is considered to have plateaued is not precisely defined, it would be reasonable to consider levels to have plateaued if they have decreased by less than 10–15%. Large decreases in hCG levels are more consistent with failed intrauterine pregnancy than ectopic pregnancy. In two small series of women undergoing uterine aspiration for pregnancy of unknown location, nearly all women with a decrease in hCG levels of 50% or greater within 12–24 hours after aspiration had failed intrauterine pregnancies (29, 40). Patients with a decrease in hCG of 50% or greater can be monitored with serial hCG measurements, with further treatment reserved for those whose levels plateau or increase, or who develop symptoms of ectopic pregnancy. Management of patients with an hCG decrease of less than 50% should be individualized, as while failed intrauterine pregnancy is more frequent, ectopic pregnancy risk is appreciable. One study (29) noted 55.6% of patients with ectopic pregnancies had an hCG decrease of more than 10%, 23.5% had a decrease of more than 30%, and 7.1% had a decrease of more than 50%. In a series of patients who had an initial decrease of hCG levels between 15% and 50% 12–24 hours after office uterine aspiration for pregnancy

of unknown location who were monitored with serial hCG measurement, 3 of 46 patients had rising or plateauing hCG levels necessitating treatment for ectopic pregnancy (41). The other patients had resolving hCG levels, and were presumed to have failed intrauterine pregnancies. Patients with an hCG decline between 15% and 50% 12–24 hours after aspiration require at least close follow-up with serial hCG measurement, with consideration of treatment for ectopic pregnancy based on clinical factors such as plateau or increase in hCG, development of symptoms, or high clinical suspicion or strong risk factors for ectopic pregnancy (29, 40, 41).

There is debate among experts about the need to determine pregnancy location by uterine aspiration before providing methotrexate (42, 43). Proponents cite the importance of confirming the diagnosis to avoid unnecessary exposure to methotrexate and to help guide management of the current pregnancy and future pregnancies (37, 42). Arguments against the need for a definitive diagnosis include concern about the increased risk of tubal rupture because of delay in treatment while diagnosis is established and the increased health-care costs associated with additional tests and procedures (43). However, with close follow-up during this diagnostic phase, the risk of rupture is low. In one large series with serial hCG measurement of women with pregnancies of unknown location, the risk of rupture of an ectopic pregnancy during surveillance to confirm diagnosis was as low as 0.03 % among all women at risk and as low as 1.7% among all ectopic pregnancies diagnosed (22). In addition, presumptive treatment with methotrexate has not been found to confer a significant cost savings or to decrease the risk of complications (44). The choice of performing a uterine aspiration before treatment with methotrexate should be guided by a discussion with the patient regarding the benefits and risks, including the risk of teratogenicity in the case of an ongoing intrauterine pregnancy and exposure to methotrexate.

► *Who are candidates for medical management of ectopic pregnancy?*

Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration (45). These patients generally also are candidates for surgical management. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks

of each approach. Women who choose methotrexate therapy should be counseled about the importance of follow-up surveillance.

Methotrexate

Methotrexate is a folate antagonist that binds to the catalytic site of dihydrofolate reductase, which interrupts the synthesis of purine nucleotides and the amino acids serine and methionine, thereby inhibiting DNA synthesis and repair and cell replication. Methotrexate affects actively proliferating tissues, such as bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue. Systemic methotrexate has been used to treat gestational trophoblastic disease since 1956 and was first used to treat ectopic pregnancy in 1982 (46). There are no recommended alternative medical treatment strategies for ectopic pregnancy beyond intramuscular methotrexate. Although oral methotrexate therapy for ectopic pregnancy has been studied, the outcomes data are sparse and indicate that benefits are limited (47).

Contraindications

Box 1 lists absolute and relative contraindications to methotrexate therapy (45). Before administering methotrexate, it is important to reasonably exclude the presence of an intrauterine pregnancy. In addition, methotrexate administration should be avoided in patients with clinically significant elevations in serum creatinine, liver transaminases, or bone marrow dysfunction indicated by significant anemia, leukopenia, or thrombocytopenia. Because methotrexate affects all rapidly dividing tissues within the body, including bone marrow, the gastrointestinal mucosa, and the respiratory epithelium, it should not be given to women with blood dyscrasias or active gastrointestinal or respiratory disease. However, asthma is not an exclusion to the use of methotrexate. Methotrexate is directly toxic to the hepatocytes and is cleared from the body by renal excretion; therefore, methotrexate typically is not used in women with liver or kidney disease.

Relative contraindications for the use of methotrexate (Box 1) do not serve as absolute cut-offs but rather as indicators of potentially reduced effectiveness in certain settings. For example, a high initial hCG level is considered a relative contraindication. Systematic review evidence shows a failure rate of 14.3% or higher with methotrexate when pretreatment hCG levels are higher than 5,000 mIU/mL compared with a 3.7% failure rate for hCG levels less than 5,000 mIU/mL (48). Of note, studies often have excluded patients from methotrexate treatment when hCG levels are greater than

Box 1. Contraindications to Methotrexate Therapy ↗**Absolute Contraindications**

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient
- Inability to participate in follow-up

Relative Contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial hCG concentration
- Ectopic pregnancy greater than 4 cm in size as imaged by transvaginal ultrasonography
- Refusal to accept blood transfusion

Modified from Medical treatment of ectopic pregnancy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. *Fertil Steril* 2013;100:638–44.

5,000 mIU/mL based on expert opinion that these levels are a relative contraindication to medical management. Other predictors of methotrexate treatment failure include the presence of an advanced or rapidly growing gestation (as evidenced by fetal cardiac activity) and a rapidly increasing hCG concentration (greater than 50% in 48 hours) (48–50).

► ***What methotrexate regimens are used in the management of ectopic pregnancy, and how do they compare in effectiveness and risk of adverse effects?***

There are three published protocols for the administration of methotrexate to treat ectopic pregnancy: 1) a single-dose protocol (51), 2) a two-dose protocol (52), and 3) a fixed multiple-dose protocol (53) (Box 2). The single-dose regimen is the simplest of the three regimens; however, an additional dose may be required to ensure resolution in up to one quarter of patients (54, 55). The two-dose regimen was first proposed in 2007 in an effort to combine the efficacy of the multiple-dose protocol with the favorable adverse effect profile of the single-dose regimen (55). The two-dose regimen adheres to the same hCG monitoring schedule as the single-dose regimen, but a second dose of methotrexate is administered on day 4 of treatment. The multiple-dose metho-

trexate regimen involves up to 8 days of treatment with alternating administration of methotrexate and folinic acid, which is given as a rescue dose to minimize the adverse effects of the methotrexate.

The overall treatment success of systemic methotrexate for ectopic pregnancy, defined as resolution of the ectopic pregnancy without the need for surgery, in observational studies ranges from approximately 70% to 95% (55). Resolution of an ectopic pregnancy may depend on the methotrexate treatment regimen used and the initial hCG level. However, there is no clear consensus in the literature regarding the optimal methotrexate regimen for the management of ectopic pregnancy. The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.

Single-Dose Versus Multiple-Dose

Observational studies that compared the single-dose and multiple-dose regimens have indicated that although the multiple-dose regimen is statistically more effective (92.7% versus 88.1%, respectively; $P=.035$) (single-dose

Box 2. Methotrexate Treatment Protocols ↩**Single-dose regimen***

- Administer a single dose of methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Measure hCG level on posttreatment day 4 and day 7
 - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
 - If decrease is less than 15%, readminister methotrexate at a dose of 50 mg/m² intramuscularly and repeat hCG level
 - If hCG does not decrease after two doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Two-dose regimen†

- Administer methotrexate at a dose of 50 mg/m² intramuscularly on day 1
- Administer second dose of methotrexate at a dose of 50 mg/m² intramuscularly on day 4
- Measure hCG level on posttreatment day 4 and day 7
 - If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level
 - If decrease is less than 15%, readminister methotrexate 50 mg/m² intramuscularly on day 7 and check hCG levels on day 11
 - If hCG levels decrease 15% between day 7 and day 11, continue to monitor weekly until reaching nonpregnant levels
 - If the decrease is less than 15% between day 7 and day 11, readminister dose of methotrexate 50 mg/m² intramuscularly on day 11 and check hCG levels on day 14
 - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Fixed multiple-dose regimen‡

- Administer methotrexate 1 mg/kg intramuscularly on days 1, 3, 5, 7; alternate with folinic acid 0.1 mg/kg intramuscularly on days 2, 4, 6, 8
- Measure hCG levels on methotrexate dose days and continue until hCG has decreased by 15% from its previous measurement
 - If the decrease is greater than 15%, discontinue administration of methotrexate and measure hCG levels weekly until reaching nonpregnant levels (may ultimately need one, two, three, or four doses)
 - If hCG does not decrease after four doses, consider surgical management
- If hCG levels plateau or increase during follow-up, consider administering methotrexate for treatment of a persistent ectopic pregnancy

Abbreviation: hCG, human chorionic gonadotropin.

*Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. *Am J Obstet Gynecol* 1993;168:1759-62; discussion 1762-5.

†Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. *Fertil Steril* 2007;87:250-6.

‡Rodi IA, Sauer MV, Gorill MJ, Bustillo M, Gunning JE, Marshall JR, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. *Fertil Steril* 1986;46:811-3.

failure OR, 1.71; 95% CI, 1.04–2.82), the single-dose regimen is associated with a decreased risk of adverse effects (OR, 0.44; 95% CI, 0.31–0.63) (55). However, a more recent systematic review of randomized controlled trials showed similar rates of successful resolution with the single-dose and multiple-dose regimens (relative risk [RR], 1.07; 95% CI, 0.99–1.17) and an increased risk of adverse effects with the multiple-dose protocol (RR, 1.64; 95% CI, 1.15–2.34) (56).

Single-Dose Versus Two-Dose

A systematic review and meta-analysis of three randomized controlled trials showed similar rates of successful resolution for the two-dose and single-dose protocols (RR, 1.09; 95% CI 0.98–1.20) and comparable risk of adverse effects (RR, 1.33; 95% CI, 0.92–1.94) (56). However, in two of the three trials included in the review, the two-dose regimen was associated with greater success among women with high initial hCG levels. In the first trial, there was a nonstatistically significant trend toward greater success for the two-dose regimen in the subgroup with an initial hCG level greater than 5,000 mIU/mL (80.0% versus 58.8%, $P=.279$) (RR, 0.74; 95% CI, 0.47–1.16) (57). The second trial reported a statistically significant higher success rate for the two-dose regimen versus the single-dose regimen in patients with initial serum hCG levels between 3,600 mIU/mL and 5,500 mIU/mL (88.9% versus 57.9%, $P=.03$) (OR 5.80; 95% CI, 1.29–26.2) (58).

► *What surveillance is needed after methotrexate treatment?*

After administration of methotrexate treatment, hCG levels should be serially monitored until a nonpregnancy level (based upon the reference laboratory assay) is reached (51). Close monitoring is required to ensure disappearance of trophoblastic activity and to eliminate the possibility of persistent ectopic pregnancy. During the first few days after treatment, the hCG level may increase to levels higher than the pretreatment level but then should progressively decrease to reach a nonpregnant level (51). Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention (51). Methotrexate treatment failure in patients who did not undergo pretreatment uterine aspiration should raise concern for the presence of an abnormal intrauterine gestation. In these patients, uterine aspiration should be considered before repeat methotrexate administration or surgical manage-

ment, unless there is clear evidence of a tubal ectopic pregnancy. Ultrasound surveillance of resolution of an ectopic pregnancy is not routinely indicated because findings do not predict rupture or time to resolution (59, 60). Resolution of serum hCG levels after medical management is usually complete in 2–4 weeks but can take up to 8 weeks (55). The resolution of hCG levels is significantly faster in patients successfully treated with the two-dose methotrexate regimen compared with the single-dose regimen (25.7+13.6 versus 31.9+14.1 days; $P>.025$) (57).

► *What are the potential adverse effects of systemic methotrexate administration?*

Adverse effects of methotrexate usually are dependent on dose and treatment duration. Because methotrexate affects rapidly dividing tissues, gastrointestinal problems (eg, nausea, vomiting, and stomatitis) are the most common adverse effects after multiple doses. Vaginal spotting is expected. It is not unusual for women treated with methotrexate to experience abdominal pain 2–3 days after administration, presumably from the cytotoxic effect of the drug on the trophoblastic tissue. In the absence of signs and symptoms of overt tubal rupture and significant hemoperitoneum, abdominal pain usually can be managed expectantly by monitoring a woman's hemoglobin level and intraperitoneal fluid amount with transvaginal ultrasonography.

Elevation of liver enzymes is a less commonly reported adverse effect and typically resolves after discontinuing methotrexate use (61). Alopecia also is a rare adverse effect of the low doses used to treat ectopic pregnancy. Cases of pneumonitis also have been reported, and women should be counseled to report any fever or respiratory symptoms to their physicians (62).

► *How should women be counseled regarding the treatment effects of methotrexate?*

Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed. It is important to educate patients about the symptoms of tubal rupture and to emphasize the need to seek immediate medical attention if these symptoms occur. Vigorous activity and sexual intercourse should be avoided until confirmation of resolution because of the theoretical risk of inducing rupture of the ectopic pregnancy. Additionally, practitioners should limit pelvic and ultrasound examinations when possible. Patients should be advised to avoid folic acid supplements, foods

that contain folic acid, and nonsteroidal antiinflammatory drugs during therapy because these products may decrease the efficacy of methotrexate. Avoidance of narcotic analgesic medications, alcohol, and gas-producing foods are recommended so as not to mask, or be confused with, escalation of symptoms of rupture. Sunlight exposure also should be avoided during treatment to limit the risk of methotrexate dermatitis (63).

Before treatment with methotrexate, women should be counseled about the potential for fetal death or teratogenic effects when administered during pregnancy. The product labeling approved by the U.S. Food and Drug Administration recommends that women avoid pregnancy during treatment and for at least one ovulatory cycle after methotrexate therapy (63). Methotrexate is cleared from the serum before the 4–12 weeks necessary for the resolution of the ectopic gestation and ovulation in the next cycle (64, 65). However, there are reports of methotrexate detectable in liver cells 116 days past exposure (66). Limited evidence suggests that the frequency of congenital anomalies or early pregnancy loss is not elevated in women who have become pregnant shortly after methotrexate exposure (66). However, perhaps based on the timing of methotrexate's clearance from the body, some experts continue to recommend that women delay pregnancy for at least 3 months after the last dose of methotrexate (67).

► ***How does methotrexate treatment affect subsequent fertility?***

Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve. A prospective observational study noted no difference in anti-müllerian hormone levels or reproductive outcomes after administration of methotrexate (68). Furthermore, a systematic review of women undergoing fertility treatment found no significant differences in the mean number of oocytes retrieved during the cycles before and after methotrexate administration (69).

► ***Who are candidates for surgical management of ectopic pregnancy?***

In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each

approach. Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

Surgical management is necessary when a patient meets any of the absolute contraindications to medical management listed in Box 1 and should be considered when a patient meets any of the relative contraindications. Surgical management should be employed when a patient who initially elects medical management experiences a failure of medical management. Surgical treatment also can be considered for a clinically stable patient with a nonruptured ectopic pregnancy or when there is an indication for a concurrent surgical procedure, such as tubal sterilization or removal of hydrosalpinx when a patient is planning to undergo subsequent in vitro fertilization.

Surgical management generally is performed using laparoscopic salpingectomy (removal of part or all of the affected fallopian tube) or laparoscopic salpingostomy (removal of the ectopic pregnancy while leaving the affected fallopian tube in situ). Laparotomy typically is reserved for unstable patients, patients with a large amount of intraperitoneal bleeding, and patients in whom visualization has been compromised at laparoscopy.

► ***How do medical management and surgical management of ectopic pregnancy compare in effectiveness and risk of complications?***

Medical management of ectopic pregnancy avoids the inherent risks of surgery and anesthesia. However, compared with laparoscopic salpingectomy, medical management of ectopic pregnancy has a lower success rate and requires longer surveillance, more office visits, and phlebotomy. Randomized trials that compared medical management of ectopic pregnancy with methotrexate to laparoscopic salpingostomy have demonstrated a statistically significant lower success rate with the use of single-dose methotrexate (relative rate for success, 0.82; 95% CI, 0.72–0.94) and no difference with the use of multidose methotrexate (relative rate for success, 1.8; 95% CI, 0.73–4.6) (70). Comparing systemic methotrexate with tube-sparing laparoscopic surgery, randomized trials have shown no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies (70).

Medical management of ectopic pregnancy is cost effective when laparoscopy is not needed to make the diagnosis and hCG values are less 1,500 mIU/mL (71). Surgical management of ectopic pregnancy is more cost

effective if time to resolution is expected to be prolonged, or there is a relatively high chance of medical management failure, such as in cases with high or increasing hCG values or when embryonic cardiac activity is detected (72, 73).

► ***How do salpingostomy and salpingectomy compare in effectiveness and fertility outcomes in the management of ectopic pregnancy?***

The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage. Randomized controlled trials that compared salpingectomy with salpingostomy for the management of ectopic pregnancy have found no statistically significant difference in the rates of subsequent intrauterine pregnancy (RR, 1.04; 95% CI, 0.899–1.21) or repeat ectopic pregnancy (RR, 1.30; 95% CI, 0.72–2.38) (74). In contrast, cohort study findings indicate that salpingostomy is associated with a higher rate of subsequent intrauterine pregnancy (RR, 1.24; 95% CI, 1.08–1.42) but also with an increased risk of repeat ectopic pregnancy (10% versus 4%; RR, 2.27; 95% CI, 1.12–4.58) compared with salpingectomy (74).

In general, salpingectomy is the preferred approach when severe fallopian tube damage is noted and in cases in which there is significant bleeding from the proposed surgical site. Salpingectomy can be considered in cases of desired future fertility when the patient has a healthy contralateral fallopian tube. However, salpingostomy should be considered in patients who desire future fertility but have damage to the contralateral fallopian tube and in whom removal would require assisted reproduction for future childbearing. When salpingostomy is performed, it is important to monitor the patient with serial hCG measurement to ensure resolution of ectopic trophoblastic tissue. If there is concern for incomplete resection, a single prophylactic dose of methotrexate may be considered (45).

► ***Who are candidates for expectant management of diagnosed ectopic pregnancy?***

There may be a role for expectant management of ectopic pregnancy in specific circumstances. Candidates for successful expectant management of ectopic pregnancy should be asymptomatic; should have objective evidence of resolution (generally, manifested by a plateau or decrease in hCG levels); and must be counseled and willing to accept the potential risks, which include tubal rupture, hemorrhage, and emergency surgery. If the initial

hCG level is less than 200 mIU/mL, 88% of patients will experience spontaneous resolution; lower spontaneous resolution rates can be anticipated with higher hCG levels (75). In a single small randomized trial of women with hCG levels less than 2,000 mIU/mL, expectant management was not associated with a statistically significant lower treatment success than single-dose methotrexate for the management of ectopic pregnancy (59% versus 76%, respectively) (RR, 1.3; 95% CI, 0.9–1.8) (76). Reasons for abandoning expectant management include intractable or significantly increased pain, insufficient decrease of hCG levels, or tubal rupture with hemoperitoneum.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- In clinically stable women in whom a nonruptured ectopic pregnancy has been diagnosed, laparoscopic surgery or intramuscular methotrexate administration are safe and effective treatments. The decision for surgical management or medical management of ectopic pregnancy should be guided by the initial clinical, laboratory, and radiologic data as well as patient-informed choice based on a discussion of the benefits and risks of each approach.
- Surgical management of ectopic pregnancy is required when a patient is exhibiting any of the following: hemodynamic instability, symptoms of an ongoing ruptured ectopic mass (such as pelvic pain), or signs of intraperitoneal bleeding.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Serum hCG values alone should not be used to diagnose an ectopic pregnancy and should be correlated with the patient's history, symptoms, and ultrasound findings.
- If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3,500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue.
- The decision to perform a salpingostomy or salpingectomy for the treatment of ectopic pregnancy

should be guided by the patient's clinical status, her desire for future fertility, and the extent of fallopian tube damage.

- ▶ The choice of methotrexate protocol should be guided by the initial hCG level and discussion with the patient regarding the benefits and risks of each approach. In general, the single-dose protocol may be most appropriate for patients with a relatively low initial hCG level or a plateau in hCG values, and the two-dose regimen may be considered as an alternative to the single-dose regimen, particularly in women with an initial high hCG value.
- ▶ Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is associated with a high risk of treatment failure and requires additional methotrexate administration (in the case of the single-dose or two-dose regimen) or surgical intervention.
- ▶ Patients can be counseled that available evidence, although limited, suggests that methotrexate treatment of ectopic pregnancy does not have an adverse effect on subsequent fertility or on ovarian reserve.
- ▶ There may be a role for expectant management of ectopic pregnancy in specific circumstances.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- ▶ The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis.
- ▶ A woman with a pregnancy of unknown location who is clinically stable and has a desire to continue the pregnancy, if intrauterine, should have a repeat transvaginal ultrasound examination, or serial measurement of hCG concentration, or both, to confirm the diagnosis and guide management.
- ▶ Medical management with methotrexate can be considered for women with a confirmed or high clinical suspicion of ectopic pregnancy who are hemodynamically stable, who have an unruptured mass, and who do not have absolute contraindications to methotrexate administration.
- ▶ After administration of methotrexate treatment, hCG levels should be serially monitored until a non-pregnancy level (based upon the reference laboratory assay) is reached.

- ▶ Patients treated with methotrexate should be counseled about the risk of ectopic pregnancy rupture; about avoiding certain foods, supplements, or drugs that can decrease efficacy; and about the importance of not becoming pregnant again until resolution has been confirmed.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and September 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

This information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations in practice may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology. The American College of Obstetricians and Gynecologists reviews its publications regularly; however, its publications may not reflect the most recent evidence. Any updates to this document can be found on www.acog.org or by calling the ACOG Resource Center.

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